REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated March 28, 2005 (the "Final Action"). Claims 1-6 and 8-24 are pending in the present application upon entry of this Amendment. Applicants respectfully submit that Claims 1-6 and 8-24 are patentable over the cited references.

I. Interview Summary

Applicants extend their gratitude to Examiner Alana M. Harris, Ph.D. for the telephonic interview conducted on October 25, 2005 with inventors Drs. Darell Bigner, Michael Zalutsky and David Rizzieri and Applicants' representatives Shawna Lemon and Kenneth Sibley.

The participants discussed U.S. Patent No. 5,624,659 to Bigner et al. (the "'659 patent"), Rizzieri et al. *Blood* **94(10)** Part 2, Supplement 1: 4339 (1999) ("Rizzieri (a)") and Abstract #4339 (1999) ("Rizzieri (b)") in view of the present application. As noted in the Interview Summary prepared by the Examiner and dated October 28, 2005, Applicants discussed the systemic, in this case, intravenous, administration of the monoclonal antibody coupled to ^{131}I, and the surprising effects of retained biological activity and therapeutic effectiveness that persisted for a prolonged period of time. The Examiner indicated that the said administration did not impart novelty or non-obviousness to the claims and that the results were not considered unexpected in view of the motivation provided by the references, i.e., the '659 patent at Col. 4, lines 16-26 and Examples showing ^{131}I conjugated to mAb 816C6 and Rizzieri et al., last paragraph.

In view of the helpful and constructive dialog expressed during this interview, Applicants set forth below additional remarks that support the novelty and non-obviousness of the pending claims.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Final Action maintains the rejection of Claims 4 and 12-22 under 35 U.S.C. §112, first paragraph, as failing to provide adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the

deposit of the biological materials. *See* Final Action, page 3. Applicants continue to respectfully disagree with this assertion.

As previously noted, the present invention is directed to the new use of a **known** compound. In particular, ^{131}I-labeled chimeric 81C6 monoclonal antibody was described in U.S. Patent No. 5,624,659 to Bigner et al. A review of the patent file reveals that a Sequence Listing under 37 C.F.R. §1.821(c) for the nucleotide and amino acid sequences described in the specification was submitted during prosecution of the application.[1] By providing the relevant sequences and the synthesis of specific antibodies for use in the patented invention, one of ordinary skill in the art is provided a repeatable method for obtaining the 81C6 antibody. Accordingly, since the present invention is directed to a new use of this compound, Applicants respectfully submit that a deposit of the molecules designated as 81C6 for patent purposes is not required in this instance where the claimed cell lines can be reproduced without "undue" experimentation.

Accordingly, Applicants respectfully submit that Claims 4 and 12-24 comply with the written description requirement and the enablement requirement of 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of these rejections.

III. Claim Rejections Under 35 U.S.C. §103

The Final Action maintains the rejection of Claims 1-6 and 8-22 under 35 U.S.C. §103(a) as being unpatentable over the '659 patent in view of Rizzieri (a) and Rizzieri (b). *See* Final Action, page 4. More specifically, the Final Action asserts that the Rizzieri declaration is not commensurate in scope with the claims in that the Rizzieri declaration focuses on the administration and the implementation of ^{131}I anti-tenascin human/mouse chimeric 81C6 monocloconal antibody in Non-Hodgkin's lymphoma treatment. *See* Final Action, page 5. The Final Action further asserts that the declaration does not provide unexpected results that render the claimed invention unobvious. *See* Final Action, page 5. Moreover, the Final Action asserts that a *prima facie* case of obviousness was established in the first action in the merits dated July 7, 2004. *See* Final Action, page 5. Similar assertions were made by the Examiner during the telephonic interview. *See* Interview Summary above.

[1] U.S. Patent Application Serial No. 08/392,419; Attorney Docket No. 5405-90A. A paper copy and computer readable copy of the Sequence Listing was submitted along with an Amendment and Response on February 28, 1994. The Sequence Listing appears in the '659 patent at columns 13 through 20.

Applicants again respectfully disagree with these assertions for reasons of record and at least in view of the reasons discussed below.

A. The Final Action and the First Action on the Merits Fail to Establish a *Prima Facie* Case of Obviousness

Regarding the '659 patent and Rizzieri (b), the Final Action asserts that "[b]ased on the combination of these reference teachings, one of ordinary skill in the art would have arrived at the claimed invention at the time with a reasonable expectation of success. Both references provide suggestion and motivation to establish and arrive at the claimed invention. . . ." Final Action, page 6.

For reasons previously set forth, Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine these references where each focuses upon different tumor types, i.e., the '659 patent being directed to treating solid and cystic tumors, in particular brain tumors, that express tenascin, and Rizzieri (b) directed to treatment of non-Hodgkin's lymphoma. However, even if these reference teachings were combined, one of ordinary skill in the art would **not** arrive at the claimed methods of treating lymphoma or non-Hodgkin's lymphoma.

As noted during the telephonic interview, two of the present inventors, Drs. Darell Bigner and Michael Zalutsky, are the named inventors of the '659 patent. These inventors attempted to utilize monoclonal antibody 81C6 to treat brain tumors by systemic administration or by carotid artery injection. Drs. Bigner and Zalutsky found that they were not able to sustain therapeutically effective levels of the delivered isotope at the desired tumor target. Consequently, Drs. Bigner and Zalutsky developed the alternate technique of injecting the labeled antibody into surgically created tumor resection cavities as provided in the '659 patent and not discussed in the present application.

Thus, the "combined teachings" of the cited references were shown to be unsuccessful in treating tumors as discussed above. Therefore, the combination of the cited references would not enable one of ordinary skill in the art to arrive at the present invention directed to methods of treating lymphoma as recited in Claims 1 and 23, or methods of treating non-Hodgkin's lymphoma as recited in Claims 12 and 22. Accordingly, Applicants respectfully submit that Claims 1-6 and 8-24 are not obvious under 35 U.S.C. § 103(a) in view of the '659

patent in combination with Rizzieri (b), and Applicants respectfully request withdrawal of these rejections.

B. The Present Inventors Have Shown Unexpected Results

Applicants respectfully maintain that a *prima facie* case of obviousness has not been established. However, assuming *arguendo*, that a *prima facie* case of obviousness has been established, Applicants have provided unexpected results that rebut the *prima facie* case.

In particular, the radiolabeled antibody was thought to be taken up by lymphoma tissue in a manner similar to that seen with normal tissue. Study results instead revealed rapid uptake in liver and marrow and a slower, but enhanced, uptake in selected tumor sites over normal organs. There was at least a 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue. Moreover, the estimated average absorbed dose to selected tumors of ^{131}I anti-tenascin chimeric 81C6 was higher than that obtained from ^{131}I-tositumomab. These unexpected results obtained from human data support methods of treating lymphoma using an antibody that binds to tenascin in a treatment effective amount as disclosed in the present application. These unexpected results were previously submitted on October 5, 2004 in the Declaration of David A. Rizzieri, M.D. Pursuant to 37 C.F.R. §1.132.

As stated in the Manual of Patent Examining Procedure (M.P.E.P.), "Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, **and** that the results are of a significant, practical advantage." M.P.E.P. §716.02(a) citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). As noted by Dr. Michael Zalutsky during the telephonic interview, the results of this particular project were further surprising because the localization of ^{131}I at the target, i.e., lymphoma was maintained for a long period of time. In fact, in some patients, the clearance of radioactivity from the lymphoma sites was close to that of the physical half-life of ^{131}I (8 days), which is the maximum tumor retention that is believed possible. Because of this, the radiation dose delivered to the tumor per unit administered activity was higher than that seen with ^{131}I-tositumomab (Bexxar®), the commercially available labeled antibody for treatment of lymphoma. Such results indicate substantially longer tumor retention than reported for other antibodies evaluated for radioimmunotherapy (anti-CEA hMN-14, anti-TAG72 CC49, A33, 17-1A, for example).

In view of these surprising results, it is important to note that there is a difference between over-expression of a target, and the ability to sustain a dose of a radioisotope at that target. Factors that play a role in addition to target molecule concentration (in this case, tenascin) are delivery, which depends on blood flow to the site, and the interstitial pressure gradient tumors which may impede the delivery of labeled molecules to tumors. *See* Hauck, M.L., Dewhirst, M.W., and Zalutsky, M.R.: Enhancement of radiolabeled monoclonal antibody uptake in tumors with local hyperthermia. In: *Targeted Delivery of Imaging Agents*. Torchilin, V.P., ed., CRC Press, Boca Raton, FL, 1995; 335-361. Degradation of the labeled molecule (labeled antibody) in the body can also play a role.

The liver contains an extremely large amount of tenascin, much more than in the target lymphoma. In this case, it was surprising that the liver did not take up the labeled antibodies to such an extent that no effective dose was sustainable at the desired target. Instead, however, it appeared that the antibody was **preferentially** taken up and retained by the target more than the liver. This was particularly surprising in light of the systemic delivery of the antibody (specifically, by intraveneous injection), which one of ordinary skill in the art would have thought would permit the liver to take up a substantial amount of the antibody because of its high blood flow. It was further surprising that, as time progressed, the preferential targeting (or uptake) of the antibody to the tumor over liver **increased**, rather than decreased. For therapy, an important aspect is the relative radiation dose delivered to the tumor compared to normal organs. This dose was calculated using multiple imaging sessions performed over a week and extrapolated to consider all decays of ^{131}I. After completion, it was discovered that the radiation dose delivered to the tumor, 0.60 cGy/MBq, was more than 5 times higher than that received by liver, 0.11 cGy/MBq. This result was unexpected and completely different from the experience when Drs. Bigner and Zalutsky attempted to systemically deliver 81C6 to the brain.

The surprisingly preferential uptake of 81C6 by the lymphoma, with systemic delivery, allows the clinician to limit the dosage of radioisotope that has to be administered to the patient. This reduced dosage may be advantageous because of the significant safety issues, as well as cumbersome and expensive handling precautions, involved in preparing and administering radioisotope labeled antibodies. Patients receiving ^{131}I labeled antibodies and other radiotherapeutic drugs are typically isolated from other individuals to avoid their

exposure to radiation. Administering lower amounts of radioactivity can lessen this problem. It also decreases exposure to staff involved in the preparation and administration of the labeled antibody as well as other health care staff involved in patient care.

Accordingly, at least in view of these unexpected results clearly presenting a significant **and** practical advantage, Applicants respectfully submit that Claims 1-6 and 8-24 are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with Rizzieri (a) and/or Rizzieri (b), and Applicants respectfully request withdrawal of these rejections.

C. Experts Expressed Skepticism Regarding Anti-tenascin Therapy

Again, assuming *arguendo*, that a *prima facie* case of obviousness has been established, Applicants offer further secondary considerations that rebut the *prima facie* case.

Studies directed to anti-tenascin therapy for the treatment of non-Hodgkin's lymphoma were met with skepticism by National Institutes of Health (NIH) reviewers. In particular, upon review of grant applications submitted by the present inventors in an effort to receive funding for their studies, grant reviewers, who were experts in the field of cancer research, stated the following, among other comments, in their denial of the applications:

> (a) The application is a correlative study on the expression of tenascin and aggressive behavior of NHL. The application concludes that the successful completion of Aims 1 and 2 will naturally lead to a Phase I trial of anti-tenascin therapy. This is an oversimplified conclusion, since a target validation would involve much more than correlating expression of a specific protein with tumor progression;
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> (b) This study needs to be undertaken if there is compelling evidence that administration of unlableled anti-tenascin antibody will improve relative tumor dose delivery. The role of an anti-stromal antibody in lymphoma is unclear in the non-myeloablative setting, and it is unclear, given the relatively low iodine-131 MTD already seen with this antibody, whether there would ever be a role for an anti-stromal antibody in a disease with well characterized surface antigens already under scrutiny; and
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> (c) Whether tenascin has anything to do with pathogenesis or is simply a marker of reactive stromal cells that coincides with recurrence . . . remains an open question, and certainly nothing in this application addresses this question. . . . . Again, one wonders about the strategy, which targets nearby stromal cells when more biologically relevant targets exist on lymphoma cells. For situations where no targets exist, or when specific antibodies are hard to

construct, this approach may have some value, but as a first line approach it lacks the biological relevance or elegance that targets on the tumor cells might have.

The skepticism expressed by the experts in this field of research further supports the non-obviousness of the methods of treating lymphoma and non-Hodgkin's lymphoma as recited in the pending claims.

Accordingly, at least in view of the skepticism expressed by experts, Applicants respectfully submit that Claims 1-6 and 8-24 are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with Rizzieri (a) and/or Rizzieri (b), and Applicants respectfully request withdrawal of these rejections.

IV. New Claims 23 and 24 Are Patentable Over the Cited References

New Claim 23 recites as follows:

> 23. A method of treating lymphoma in a human subject in need thereof, comprising:
> administering intravenously to a subject afflicted with lymphoma an antibody that binds to tenascin in a treatment effective amount, wherein said antibody is coupled to a radioisotope and retention of said antibody in the lymphoma is at least two-fold greater compared to normal tissue.

New Claim 23 recites as follows:

> 24. (New) A method according to claim 12, wherein said antibody is a murine monoclonal antibody 81C6.

Applicants respectfully submit that the cited references do not teach or suggest the recitations of new Claims 23 or 24. In particular, at least in view of the discussions above, the cited references do not teach or suggest that a radiolabeled antibody that binds to tenascin can be retained at the target lymphoma site in a concentration that is at least two-fold greater compared to normal tissue as recited in Claim 23. Support for this new claim can be found in the Present Application on page 23, lines 1-8 and at Table 6. Further, clinical studies with brain tumor patients conducted by Applicants have led Applicants to believe that the murine 81C6 antibody may present a desirable blood clearance which may lessen the chance of hematologic toxicity. Support for this new claim can be found at page 3, lines 1-3.

Accordingly, Applicants respectfully submit that new Claims 23 and 24 are patentable, and Applicants respectfully request entry and allowance thereof.

V. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

It is not believed that any fee(s), including fees for additional claims, are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that additional fees are necessary to allow consideration of this paper, such an extension is also hereby petitioned for under 37 C.F.R. §1.136(a). Applicants authorize that any additional fees believed to be due in connection with this paper may be charged to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 CFR § 1.8

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office via facsimile number 571-273-8300 on December 8, 2005.

Susan E. Freedman
Date of Signature: December 8, 2005